The Origin of Death and Aging

Many ancestral life forms seem to be immortal: single celled (clones), sponges, jellyfish, corals, hydra, flatworms (animals that can regenerate).

Cancers are immortal. Hayflick limit.

So death doesn't seem necessary…

Origin of programmed cell death

- Earliest lifeforms (3 by) - cyanobacteria – algal blooms – die overnight - on purpose.
- Programmed cell death – same signaling pathways to us – caspase enzymes – complex cascade– principle broker of death is the mitochondria (1000s/cell, energy) – it launches an army of molecular executioners. --*Why?*
- Viruses - <100 billion in every litre of seawater. >100X number of bacteria. (similar in ancient times). Every day, these viruses kill about half of all the bacteria in the world's oceans. This unceasing war is the most significant force in evolution. Programmed death was the first weapon. [evolved out of the toxin plus antidote]
- Same for any physical threat like UV radiation – few spore cells survive while the others committee suicide. Avoids passing on deleterious mutations.
- KEY principle (as you'll see) – *this is the origin of death, relevant to us now...*

Programmed death makes multicellular life possible

– eg colony - ball with flagella on outside and spore cells inside. Germ cells and somatic cells. The germ line is immortal, while the rest of the cells are expendable. In complex multicellular life, cell types must remain committed to their role, for the good of the whole, and not malfunction or go independent [CANCER]. Must have a POLICING system to enforce this using cell death. *"Only death makes multicellular life possible. If organisms didn't die there would be no evolution and we wouldn't be here. We owe or lives to death."*

"Death settings" are a fine line – if less likely, result is cancer. If too likely, degeneration. *In aging, both things happen at once. Why?*

To understand ageing in terms of natural selection – two important factors:

(1) Importance of the reproductive period

Even if immortal, accidents happen and the chances of dying increase with age – "statistically probable lifespan". So individuals that concentrate their reproductive resources in earlier part of life are more likely to have more offspring than those that take their time.

In higher animals, lifespan is correlates with the timing of the reproductive period (except bird and bats). Fruit flies short lived, but mortality rate looks same as ours c.f. reproductive period. Sea turtles puberty at 50 and reproduce for 100 years, live about 200 years. Bowhead whale even longer.

(2) Concept of antagonistic pleiotropy – (relev for diseases of aging)

Such a gene that gives a small degree of reproductive success is selected for and remains in the genome, even though it causes dreadful degeneration later on.

Genes that cause bad things like Alzheimer's or heart disease can't be eliminated by natural selection because the bad thing occurs ***after*** the reproductive period (after we're "statistically dead"). Net result is natural selection "***promotes"*** the **diseases of aging**.

And now humans have prolonged our life expectancy so we've "*disinterred a graveyard of genes, and they pursue us to our graves.*"

So the diseases of aging are "triggered" or "unmasked" by aging. They're not on a timer. So slowing aging will postpone the diseases.

[But what is the cause of aging itself, and death of the whole organism?---]

We know something about---

Control of lifespan

1. Found one mutation doubles lifespan in all life forms. It also postpones the diseases of aging.

2. Shows aging is determined by the same biochemical pathways in yeast, flies, and mice.
3. Therefore it should be easier to cure aging (and the diseases of aging) with a single treatment than to cure any one age-related disease.
4. Those mutations control the pathways for **sexual maturation**.
5. Reproducing requires resources, can only happen in times of plenty. The main signal is **insulin**. If the signal is low, aging is put on hold until it's time to invest in reproducing. Starvation prolongs life but makes you infertile—trade-off between sex and longevity. Salmon invest everything in sex and immediately die.

We know something about---

Control of death – (*mitochondria again)*

1. Level of free radicals is a signal that controls cell physiology. Changes in the level act as a kind of alarm.
2. Main signal for programmed cell death is increased leakage of free radicals from mitochondria. The cell kills itself.
3. Lifespan varies with rate of fee radical leak. Smaller animals have higher metabolic rate, short lifespans. Large animals, slow metabolisms, long lifespans.
4. [Exception is birds and bats, who somehow keep their leak 10X slower than expected— they live longer than expected and avoid the diseases of aging. Pidgeon lives 10X longer than a rat.]
5. Again **antagonistic pleiotropy –** free radical signaling optimizes health when young, but is detrimental when old. The mitochondria wear out, free radical leak increases, trips alarm→mild inflammation→programmed cell death.
6. Caloric restriction reduces free radical leak, turns off the alarm, and resets the cells to "youth."
7. Also there are people in Japan with a mutation in mitochondrial DNA that halves the risk of disease and doubles life expectancy (1998).

The mitochondrial "glitch" in evolution – and what to do about it

Aubrey de Grey's discovery -- and solution to end aging:

- Endosymbiogenesis. (Lynn Margulis) - mtDNA.

- Throughout the course of evolution, over a thousand mt genes migrated to the nucleus.
- Only 13 protein-coding genes still reside in mitochondria. Bad place to be.
- It was the hydrophobicity of the remaining proteins. They couldn't be unfolded to import into the mitochondria.
- Then came a change in the mtDNA code itself. Independent evolution, selected for more efficient and fewer tRNAs for only transcribing these few proteins. This stopped the remaining ones from being able to be expressed in the nucleus.
- The mtDNA that remains accumulate a lot of mutations because of the proximity to free radicals.
- These mt are not weeded out by the cell's normal cleanup machinery because it can't recognize the change on the outer mt membrane. In fact these mutants show less damage, and so the older non-mutated ones are weeded out instead--A MAJOR GLITCH IN EVOLUTION!
- His solution is artificially inserting the 13 mt genes into the nucleus, modified in such a way that they can be correctly transcribed and the protein products can be imported into the mt, finishing what nature started.
- He got a PhD in gerontology simply by teaching himself biology and proposing this astonishing thesis.
- In 2007 they got a workable method to import these, using a modification of co-translational import. Or may be able to do direct RNA import, which may or may not get translated correctly by the changed mitochondrial translation system.

[18 min. x 2 = 36 min.]

Longevity and Genetics conference

A new era in human aging --public health sociologist

1. Body is built for short term use.
2. Diseases after reproduction are fundamentally linked to biological aging. It's folly to treat them like they're all unrelated. If you cured cancer, you'd just increase the risk of Alzheimer's and heart disease. Approach running out of steam now, and may even be harmful.
3. We virtually eliminated death from external causes during first half of life, so now there's twice as many people experiencing the diseases of aging, and the human life span is *not increasing (as was predicted 15 years ago; world record has not increased for 17 years*). We're producing a large global population living in frailty and disability for decades. Called "silver tsunami." Not what we intended. [True worldwide on average.]
4. There is no genetic program setting maximum lifespan, only biomechanical constraints, so **he says** we *can't* extend maximum lifespan, and life expectancy cannot go up any further. All such claims in the media or by insurance companies are bogus, known for last 25 years.
5. Medicine follows an infectious disease model; We need to supplement it with a new model that attacks the origin of aging itself. PROBLEM is that government funding for research is all disease specific, wrong priority. The only thing to focus on is reducing the underlying biological causes of aging, which is what causes the diseases of aging – **increasing healthspan, not lifespan**.

So… how to slow rate of aging …? [NEXT 3 PRESENTERS]

STUDY: Super seniors 85-108 (BCCA)

Human longevity is complex—only 30% genetic.

Physically active; up to 4 drinks/day

Not correlated --

- NOT longer telomeres (just less variance, assoc cancer)
- NOT aging gene candidates (except APOE4 Alzheimer's, of course)

- NOT protein coding genes associated with diseases of aging (THUS regulatory genes, junk DNA, and epigenetics)
- ONLY Less neuroticism

STUDY: Super centenarians (110-113, ~60 in world)

Lifespan NOT associated with lifestyle, diet, supplements, or environment; many drank multiple/day.

- Less neuroticism
- Epigenetic silencing… Methylation normally increases at 1%/year; predicts your age within 5% accuracy. But super centenarians **stop methylating** (KEY) [modulation of chromatin toward a more relaxed state, secondary to histone code]

Aubrey de Grey –rejuvenation biotechnology - his second idea

SNPs defined as minority version being at least 5% of population. Rarer SNPs have been ignored.

We've found SNPs with protective effects in many genes, but only one variant has a clinically meaningful effect, APOE4, the others are tiny effects, irrelevant .

So his idea is that super seniors depend NOT on a lucky collection of SNPs, but on having a variant that's extremely rare and unidentified. Rarely get 2 or more together. Not selected ***for*** because they act after the reproductive period, so they stay rare. We're starting to find some such rare protective genes now (one against APOE4).

Biotechnology could make this happen for everyone. Could even make more than 2 together, and go past record of 119 to maybe 140. Some may be rejuvenative, even after age 70.

(save for discussion period…)

[oldest proven case 122 years, 1997]

Metabolic Syndrome = accelerated aging (new idea)

MetS = obesity/diabetes/cardiovascular-disease (in 40% of thin people, too, as visceral fat). Main mechanism is breaking down muscle to make glucose (overexpression of genes). Alzheimer's similar process. Treating it: muscle building, protein, and timing of calories – don't eat at night. Future aging cure: looking at genes that are basis of MetS, why some need no exercise others need 4 hrs day.

REPERCUSSIONS OF LIFE EXTENSION

- The cost of longevity treatments would be far less than the current costs of futile treatments for the diseases of aging.
- Boost economy because of increased working years.
- The birth rate is currently double the death rate, so halving the birth rate balances out a world with longevity.
- also the change will occur gradually and not in isolation; the system changes and adapts.
- the therapy could postpone or eliminate menopause, allowing women to space out their pregnancies over more years and thus decreasing the yearly population growth rate.
- the fact the worldwide population growth rate is slowing down and is projected to eventually stabilize and begin falling, superlongevity would be unlikely to contribute to overpopulation